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Previews

Cell Shape by Coercion: Par1 and aPKC Put the Squeeze on Junctions

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Epithelial sheets form the basic architectural unit of most tissues and organs. To form complex organs, these sheets are folded and reshaped by cell-shape changes. Reporting recently in *Nature*, Wang et al. (2012) describe a myosin-independent mechanism that links the regulation of apical-basal polarity to tissue morphogenesis.

To build the body, cells must undergo dramatic cell-shape changes. When multiple cells coordinately change their shape, they reshape tissues and organs. Perhaps the most striking example is gastrulation, which reshapes the simple ball of cells created by zygotic cell divisions into a complex three-layered embryo with anterior-posterior and dorsal-ventral axes. One common cell-shape change that plays a key role in gastrulation is apical constriction, in which columnar cells constrict their apical ends (Sawyer et al., 2010). This process can lead to tissue folding, driving events from gut invagination to neural tube formation. The current model for apical constriction involves constriction of the actomyosin cytoskeleton linked to cell-cell adherens junctions (Figure 1). In a recent issue of *Nature*, Wang et al. (2012) expand this paradigm, identifying a mechanism driving apical constriction that involves proteins best known for setting up apical-basal polarity.

Apical-basal polarity, which makes the two sides of epithelial sheets distinct, is a conserved property of epithelia. This polarity is critical for the function of mature epithelia as regulated barriers between body compartments, but during morphogenesis it also regulates cell-shape change. Apical-basal polarity is maintained by polarized cues that define different cellular compartments (St Johnston and Ahringer, 2010; Figure 1A). The apical domain is maintained by two protein complexes: aPKC/Par6 (acting at times with Par3) and Crumbs/Stardust/Pals (Figure 1A). The basolateral domain, in turn, is maintained by the Dlg/Scribble/Lgl complex and the serine-threonine kinase Par1. Cadherin-catenin complexes form adherens junctions at the interface between these domains. Mutually antagonistic interactions between apical and basolateral complexes maintain polarity.

Drosophila apical-basal polarity is initiated in an unusual way. Early fly embryos are syncytia of many nuclei in a single cytoplasm. These are simultaneously incorporated into 6,000 cells as membranes invaginate around them in the process of cellularization. During cellularization, the apical landmark Par3 (fly Bazooka) directs apical adherens junction assembly (Harris and Peifer, 2004). As cellularization is completed, other apical and basolateral players initiate action, maintaining and elaborating polarity, and gastrulation begins.

Although Bazooka and aPKC/Par6 can form a complex, in epithelial cells aPKC/Par6 localize apically to Bazooka, which localizes to adherens junctions (Harris and Peifer, 2004; Figure 1A). Bazooka restriction to this discrete region is controlled by its phosphorylation. aPKC phosphorylates Bazooka at the apical side of cells, disrupting Bazooka cortical localization (Morais-de-Sá et al., 2010; Walther and Pichaud, 2010) and segregating Bazooka from aPKC/Par6 in the apical domain. What restricts Bazooka laterally so that it only accumulates at adherens junctions? Par1 kinase activity is key. Loss of Par1 disrupts epithelial organization, with apical proteins localizing uniformly around the cortex. Bazooka is directly phosphorylated by Par1 at sites distinct from those phosphorylated by aPKC; this also releases Bazooka from the cortex. When Bazooka cannot be phosphorylated by Par1, it is not restricted to adherens junctions but rather extends down the entire lateral cell cortex (Benton and St Johnston, 2003). Thus phosphorylation by both aPKC and Par-1 tightly regulates Bazooka localization, confining it to adherens junctions. How Bazooka is stabilized at adherens junctions remains unknown—perhaps this occurs via cadherin association.

Wang et al. examine how cells in gastrulating fly embryos form dorsal transverse folds. They find that these cells apically constrict in a coordinated way, with the position of constricting cells dictated by transcription factors specifying anterior-posterior cell fate. The textbook model suggests that apical constriction is driven by a contractile actin ring linked to adherens junctions by the catenins. In fact, this paradigm was recently altered. We now know that in many cases of apical constriction, the key contractile apparatus is an apical actomyosin network undergoing cyclical contraction, which is linked to junctions by multiple connectors (Figure 1C; Harris et al., 2009). However, Wang et al. provide data suggesting that the cell-shape change they study is not driven by actomyosin contractility—there was no difference in apical myosin localization or contractility between constricting cells and their neighbors. What drives this cell-shape change? The authors next examine adherens junctions. In cells forming dorsal folds, both adherens junctions and Bazooka shift basally (Figures 1B and 1D).

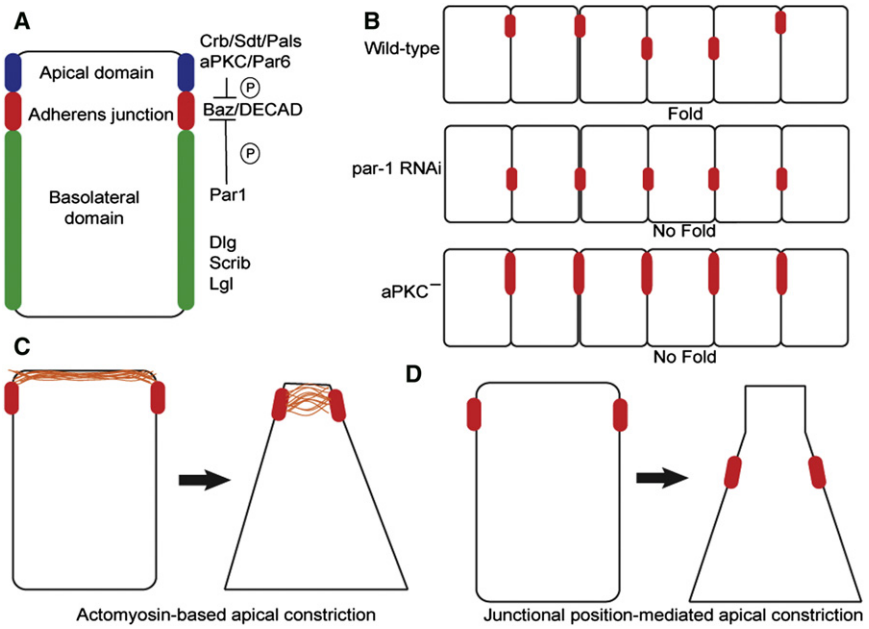

Figure 1. Roles for Cell Polarity Proteins in Junction Positioning
(A) Localization of polarity proteins in a simple epithelial cell. aPKC inhibits Bazooka (Baz) apical localization, and Par1 inhibits basolateral Bazooka localization.
(B) Baz/Cadherin (DECAD) position in wild-type, Par-1 RNAi, or *aPKC* mutant dorsal epithelia.
(C) Canonical apical constriction model, driven by actomyosin contractility.
(D) Model of apical constriction driven by positioning Bazooka and adherens junctions.

Wang et al. therefore explore the mechanisms driving basal movement of Bazooka, beginning with aPKC and Par1, which normally help to position Bazooka. They discover that a subtle but significant reduction in Par1 levels occurs specifically in dorsal-fold cells (Figure 1B). To test whether this decrease in Par1 allows Bazooka and adherens junctions to move basally, the authors examine junction position after RNAi knockdown. Interestingly, globally reducing Par1 results in junctions even more basal than those in wild-type initiating cells; furthermore, junctions localized more basally across the entire epithelium (Figure 1B), and dorsal folding was blocked. Similarly, expressing a mutant form of Bazooka that cannot be phosphorylated by Par1 blocks dorsal folds. Therefore, Par1 levels determine how far Bazooka is "pushed" apically. For Bazooka to localize to discrete rings around cells at the adherens junction level rather than covering the entire apical end of cells, however, there must also be something "pushing" it basally. aPKC was a good candidate. Wang et al. find that, whereas aPKC is not required for the basal shift of junctions, it is required for disassembling junctions apically. Therefore, in *aPKC* mutants, whereas the basal junction border drops, the junctional domain expands apically and dorsal folds do not form (Figure 1B). The authors propose that decreased Par1 levels in initiating cells allow basal movement of junctions specifically in those cells. As the basal margin of the junctions drops, the apical margin is pushed downward by disassembly in an aPKC-dependent manner. Thus, the ratio of Par1:aPKC activities is key for positioning junctions.

These data are exciting, and they suggest a mechanism that mediates one of the best-studied cell-shape changes. It is not clear, however, how shifting junctional position in a subset of cells leads to cell-shape change. The authors suggest that the increased apical domain may be inherently unstable, and its shrinkage might shorten cells and drive buckling (Figure 1D). They also propose that mechanical linkage between junctions in shortened cells and nonshortened neighbors may drive sheet curvature. It remains possible, however, that repositioned junctions stimulate a different sort of myosin-mediated contractility: similar expanded apical domains are found in mutant cells lacking adherens junctions and retaining Bazooka, and those cells contract at the position of the Bazooka ring (Harris and Peifer, 2004). Further, Bazooka and aPKC can regulate actomyosin contractility (David et al., 2010). It remains to be seen whether other tissues use similar mechanisms to mediate this or other cell-shape changes; expanding our focus beyond the handful of well-studied models of apical constriction will help address this question and may offer new surprises. Finally, it will be interesting to see whether the same cues positioning Bazooka and other polarity players in the apical-basal axis act in other contexts. It is becoming increasingly clear that proteins regulating apical-basal polarity also regulate other cellular events, e.g., modulating asymmetric division of neural stem cells, playing roles in planar polarity, by becoming differentially distributed in epithelial cells perpendicular to the apical-basal axis. In this latter role, they drive events as diverse as convergent extension and collective cell migration (St Johnston and Sanson, 2011).

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